From the:
INTER' TIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	17 FEB 2006
Applicant's or agent's file reference 12510140/EJH/AC	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/AU2004/001440	20 October 2004	21 October 2003

Applicant

MELBOURNE HEALTH et al

The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translations to those Offices.

REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the *PCT Applicant's Guide.*

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed invention is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the IPEA/AU	Authorized officer
USTRALIAN PATENT OFFICE O BOX 200, WODEN ACT 2606, AUSTRALIA -mail address: pct@ipaustralia.gov.au acsimile No. (02) 6285 3929	LEXIE PRESS Telephone No. (02) 6283 2677

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

›plicant's or agent's file reference 510140	FOR FURTHER ACTION	See Form PCT IPEA/416
ernational application No. CT/AU2004/001440	International filing date *(day/month/year)* 20 October 2004	Priority date *(day/month/year)* 21 October 2003

ernational Patent Classification (IPC) or national classification and IPC

Int. Cl.

C12N 7/00 (2006.01) *C07K 14/02* (2006.01) *C12Q 1/70* (2006.01)

›plicant

MELBOURNE HEALTH et al

This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.

This REPORT consists of a total of 9 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, comprising:

[X] *(sent to the applicant and to the International Bureau)* a total of 13 sheets, as follows:

[X] sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).

[ ] sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.

[ ] *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

This report contains indications relating to the following items:

[X]	Box No. I	Basis of the report
[ ]	Box No. II	Priority
[X]	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
[ ]	Box No. IV	Lack of unity of invention
[X]	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
[X]	Box No. VI	Certain documents cited
[ ]	Box No. VII	Certain defects in the international application
[X]	Box No. VIII	Certain observations on the international application

e of submission of the demand	Date of completion of this report
August 2005	14 February 2006
ne and mailing address of the IPEA/AU	Authorized Officer
STRALIAN PATENT OFFICE BOX 200, WODEN ACT 2606, AUSTRALIA ail address: pct@ipaustralia.gov.au	LEXIE PRESS Telephone No. (02) 6283 2677

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/AU2004/001440

Box No. I Basis of the report

With regard to the language, this report is based on:

[X] The international application in the language in which it was filed

[ ] A translation of the international application into , which is the language of a translation furnished for the purposes of:

- [ ] international search (under Rules 12.3(a) and 23.1 (b))
- [ ] publication of the international application (under Rule 12.4(a))
- [ ] international preliminary examination (Rules 55.2(a) and/or 55.3(a))

With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

[ ] the international application as originally filed/furnished

[X] the description:

pages 1-72 as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

[X] the claims:

pages as originally filed/furnished
pages* as amended (together with any statement) under Article 19
pages* 73-85 received by this Authority on 22 August 2005 with the letter of 22 August 2005
pages* received by this Authority on with the letter of

[X] the drawings:

pages 1-55 as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

[X] a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

[X] The amendments have resulted in the cancellation of:

- [ ] the description, pages
- [X] the claims, Nos. 53-130
- [ ] the drawings, sheets/figs
- [ ] the sequence listing *(specify)*:
- [ ] any table(s) related to the sequence listing *(specify)*:

[ ] This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- [ ] the description, pages
- [ ] the claims, Nos.
- [ ] the drawings, sheets/figs
- [ ] the sequence listing *(specify)*:
- [ ] any table(s) related to the sequence listing *(specify)*:

If item 4 applies, some or all of those sheets may be marked "superseded."

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos.: **1-17, 19-45, 47, 48 and 50-52 (partially)**

because:

☐ the said international application, or the said claims Nos.
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos.
are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos.
are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*

☒ no international search report has been established for said claim Nos. **1-17, 19-45, 47, 48 and 50-52 (partially as they relate to rt180L**

☐ A meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ Furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ Furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Preliminary Examining Authority in a form and manner acceptable to it.
- ☐ Pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b) and 13*ter*.2.

☐ A meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Preliminary Examining Authority in a form and manner acceptable to it

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY	International application No. PCT/AU2004/001440

x No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Statement		
Novelty (N)	Claims 2, 19, 36, 38, 40, 47 (partially)	YES
	Claims 1, 3-18, 20-35, 37, 39, 41-46 and 48-52	NO
Inventive step (IS)	Claims 2, 19, 36, 38, 40, 47 (partially)	YES
	Claims 1, 3-18, 20-35, 37, 39, 41-46 and 48-52	NO
Industrial applicability (IA)	Claims 1-52	YES
	Claims	NO

Citations and explanations (Rule 70.7)

The following documents identified in the International Search Report have been considered for the purposes of this report:

D1: WO 2003/087351 A1 (MELBOURNE HEALTH) 23 October 2003.

D2: WO 2003/066841 A1 (MELBOURNE HEALTH) 14 August 2003.

D3: WO 2004/031224 A2 (GILEAD SCIENCES, INC.) 15 April 2004.

D4: WO 2000/061758 A1 (NORTH WESTERN HEALTH CARE NETWORK) 19 October 2000.

D5: TORRESI. J., et al; Virology (2002); Vol 299: 88-99.

D6: ONO. S. K., et al; Journal of Clinical Investigation (2001), 107(4): 449-455.

NOVELTY

The invention defined in claims relates to

-HBV variants that are resistant to nucleotide analogs that have mutations in the viral DNA polymerase and in the surface antigen,

-methods of determining the potential for an HBV to exhibit reduced sensitivity to nucleotide analogs,

-methods of detecting agents that inhibit HBV variants that exhibit reduced sensitivity to nucleotide analogs,

- a computer product that assesses the likely usefulness of HBV variant

-use of HBV variants in the manufacture of medicaments,

-methods of detecting HBV variants that exhibit altered immunological profiles and

-kits for assaying HBV variants that are resistant to nucleotide analogs ADV, LMV, TFV, FTC and combinations of these.

A number of citations disclose HBV variants that exhibit resistant to nucleotide analogs that have mutations in the viral DNA polymerase and in the surface antigen.

Continued in Supplemental Box

x No. VIII Certain observations on the international application

e following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully pported by the description, are made:

aims 1-17, 19-45, 47, 48 and 50-52 are not clear, the claims refer to a mutation in the HBV DNA polymerase-80I.. It is not clear what amino acid is mutated to L at position 180 of the reverse transcriptase part of the lymerase. As such, no comment is made on the novelty and inventive step of these claims as regards this mutation.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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pplemental Box Relating to Sequence Listing

ntinuation of Box No. I, item 2:

With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:

a. type of material
- [X] a sequence listing
- [ ] table(s) related to the sequence listing

b. format of material
- [X] on paper
- [X] in electronic form

c. time of filing/furnishing
- [ ] contained in the international application as filed
- [ ] filed together with the international application in electronic form
- [ ] furnished subsequently to this Authority for the purposes of search and/or examination
- [ ] received by this Authority as an amendment* on

[ ] In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

Additional comments:

If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/AU2004/001440

ox No. VI Certain documents cited

Certain published documents (Rule 70.10)

Application No. Patent No.	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month, ear)
WO 2004/031224	15 April 2004	1 October 2003	1 October 2002

'O 2004/031224 teaches of HBV variants resistant to ADV and LMV that have the mutations rtA181V, rtN236T, A181T and sL173F, as such claims 1, 3, 4, 18, 20, 21 and 52 (claims 18 and 19 of the citation) are anticipated by the tation. The citation, however, was published after the priority date of the invention and therefore cannot be used as a ivelty or inventive step citation. However, should the validity of the present application's priority come into question, e citation may become relevant.

Non-written disclosures (Rule 70.9)

Kind of non-written disclosure	Date of non-written disclosure (day/month/year)	Date of written disclosure referring to non-written disclosure (day/month/year)

upplemental Box V

case the space in any of the preceding boxes is not sufficient.

ontinuation of Novelty:

1 teaches of HBV variants with decreased sensitivity to LMV, ADV, TFV and FTC. It also teaches of HBV resistant a combination of these analogs as disclosed in claim 1 of the invention. The HBV variants of the citation contain utations in the HBV DNA polymerase as well as in the surface antigen. The citation also teaches of methods of termining potential HBV variants that have reduced sensitivity to the agents, methods of detecting agents that inhibit e HBV variants, a computer product that assesses the likely usefulness of HBV variant. The citation discloses DNA lymerase mutations rtN139K and rtA181 and surface antigen mutants sL173F and sI195M. Claims 48 and 49 of the vention relate to kits that have known integers including the HBV variants disclosed in the citation. As such the tation discloses all the essential features of claims 1, 3-18, 20-35, 37, 39, 41-46 and 48-52 and therefore these claims e not novel.

2 also teaches of HBV variants with decreased sensitivity to LMV and ADV that contain mutations in the HBV DNA lymerase as well as in the surface antigen. The citation also teaches of methods of determining potential HBV riants that have reduced sensitivity to LMV, agents that inhibit LMV resistant variants, a computer product that sesses the likely usefulness of HBV variant. The citation also discloses DNA polymerase mutations rtM204V, 180M and rtS135Y and surface antigen mutants sQ30K, sI195M and sT115T/S. As such the citation discloses all the sential features of claims 1, 4, 18, 21, 35, 37, 39, 41-45 and 48-52.

3 teaches of HBV variants resistant to ADV and LMV that have the mutations rtA181V, rtN236T, rtA181T and 173F, as such claims 1, 3, 4, 18, 20, 21 and 52 (claims 18 and 19 of the citation) are anticipated by the citation. The ation, however, was published after the priority date of the invention and therefore cannot be used as a novelty or ventive step citation. However, should the validity of the present application's priority come into question, the citation ay become relevant.

4 discloses HBV variants that have mutations in the DNA polymerase and are resistant to the nucleotide analog LMV age 19 lines 28-30), therefore claims 1, and 4 are not novel in light of this citation. The citation also teaches of using BV variants, and in particular variants that have mutations in the surface antigen from amino acids 67 to 226, in mpositions for the prophylaxis and treatment of HBV infections (page33 line 20 – page 35, claims 31-33), as such all e essential features of claim 44 of the invention are disclosed by the citation and therefore these claims are not novel.

5 teaches of HBV variants that are resistant to LMV and carry the mutation rtL180M, as such claims 1, and 5 are not vel.

6 teaches of LMV resistant HBV mutants that have mutations at amino acids M552 and L528. These mutations rrespond to mutations rtM204V and rtL180M of the invention therefore claims 1, 4, and 37 are not novel; in light of s citation. Further the citation also teaches of a method of detecting an agent that inhibits the LMV resistant HBV tants M552 and L528 (Page 451, col 1, para 1) and as such claim 39 is not novel.

ntinued in Supplemental Box

Supplemental Box V

case the space in any of the preceding boxes is not sufficient.

Continuation of Inventive Step:

INVENTIVE STEP:

Claim 44 is not inventive in light of the citation D5. The claim relates to methods of detecting variant HBV exhibiting an altered immunological profile by contacting the HBV variants to antibodies of surface antigens and screening for altered binding..
D5 teaches of HBV variants with reduced antigenicity that are resistant to LMV (Page 93, discussion to page 94, col 1, para 1). As such, the citation clearly discloses the concept of HBV variants that have altered immunological profiles and once this is known it would be obvious to the PSA to use the standard procedures disclosed in the claims to detect the said variants. Therefore the PSA would directly and without difficulty, by routine steps, have produced the claimed invention, and therefore the claimed invention lacks an inventive step.

Claims 48 and 49 do not involve an inventive step. The claims include kits that contain genetic agents capable of detecting altered DNA polymerase and/or the surface antigen of HBV variants, or antibodies that are capable of binding to HBV surface antigen. The components that are included in the kit are not novel, a number of citations (D1-D6) disclose HBV variants that have altered DNA polymerase and/or the surface antigen which show reduced sensitivity to nucleotide analogs, further the other components of the kit – genetic agents, antibodies to the surface antigen, PCR reagents and immobilised oligonucleotides or oligopeptides are also known. As such, putting together known integers to make a kit does not involve an inventive step.

PCT/AU2004/001440
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CLAIMS

1. An isolated Hepatitis B virus (HBV) variant wherein said variant comprises a nucleotide mutation in a gene encoding a DNA polymerase resulting in at least one amino acid addition, substitution and/or deletion to said DNA polymerase and wherein said variant exhibits decreased sensitivity to one or more nucloside or nucleotide analogs selected from the list consisting of ADV, LMV, TFV or FTC; ADV and LMV; ADV and TFV; LMV and TFV; FTC and ADV; FTC and TFV; FTC and LMV; ADV and LMV and TFV; ADV and FTC and TFV; TFV and FTC and LMV; ADV and LMV and FTC; ADV and FTC and LMV and TFV, and other nucleoside or nucleotide analogs, and/or anti-HBV agents wherein said variant comprises a mutation in the DNA polymerase selected from the list consisting of rtT38K, rtA181V, rtR55H, rtY245H, rtS/T78S, rtV80L; rtN/S118N, rtN/K139K, rtE142V, rtA/T181A, rtI204M, rtQ/P/S/Stop215S, rtE/K21E, rtN/H238H, rtT128N, rtN236T, rtL180M, rtM204V, rtQ215S, rtT128S, rtN238T, rt180L, rtI204M, rtN238T, rtI187V, rtN248Q, rtS256G, rtI122V, rtA181T, rtL180M, rtA/V200V, rtM204V, rtV214A, rtH237H/P, rtV253G, rtN238T/A, rtN238T, rtN123N/I, rtS135Y, rtV214A/V and rtQ215Q/P/Stop/S.

2. The isolated HBV of Claim 1 wherein the variant comprises a mutation in the surface protein selected from the list consisting of sQ30K, sE44G, sA47T, sI126T, sA159V, sL173F, sF55S, sC/Stop69C, sC/Y76Y, sI/V110I, sN/T131N, sN134Y, sStop/W172W, sStop/W196W, sS/R207R, sV14A, sL95W, sV96G, sI208T/I, sL95W, sL196W, sT47A, sW172Stop, PreS2 T6S, sT47A, sP62L, sL/F192F, sI195M, sS53L, sL42R, SQ102Q/R, sT115T/S, sS207S/R, sL215R and sL216 stop.

3. The isolated HBV variant of Claim 1 or 2 wherein the decreased sensitivity is in respect of ADV.

4. The isolated HBV variant of Claim 1 or 2 wherein the decreased sensitivity is in respect of LMV.

5. The isolated HBV variant of Claim 1 or 2 wherein the decreased sensitivity is in respect of TFV.

6. The isolated HBV variant of Claim 1 or 2 wherein the decreased sensitivity is in respect of FTC.

7. The isolated HBV variant of Claim 1 or 2 wherein the decreased sensitivity is in respect of ADV and LMV.

8. The isolated HBV variant of Claim 1 or 2 wherein the decreased sensitivity is in respect of ADV and TFV.

9. The isolated HBV variant of Claim 1 or 2 wherein the decreased sensitivity is in respect of LMV and TFV.

10. The isolated HBV variant of Claim 1 or 2 wherein the decreased sensitivity is in respect of ADV and FTC.

11. The isolated HBV variant of Claim 1 or 2 wherein the decreased sensitivity is in respect of FTC and TFV.

12. The isolated HBV variant of Claim 1 or 2 wherein the decreased sensitivity is in respect of FTC and LMV.

13. The isolated HBV variant of Claim 1 or 2 wherein the decreased sensitivity is in respect of ADV and LMV and TFC.

14. The isolated HBV variant of Claim 1 or 2 wherein the decreased sensitivity is in respect of ADV and TFV and FTC.

15. The isolated HBV variant of Claim 1 or 2 wherein the decreased sensitivity is in respect of LMV and TFV and FTC.

16. The isolated HBV variant of Claim 1 or 2 wherein the decreased sensitivity is in respect of ADV and LMV and FTC.

17. The isolated HBV variant of Claim 1 or 2 wherein the decreased sensitivity is in respect of ADV and FTC and TFV and LMV.

18. An isolated HBV variant comprising a nucleotide mutation in the S gene resulting in at least one amino acid addition, substitution and/or deletion to the surface antigen and which exhibits decreased sensitivity to one or more nucleoside or nucleotide analogs selected from the list consisting of ADV, LMV,TFV or FTC; ADV and LMV; ADV and TFV; LMV and TFV; FTC and ADV; FTC and TFV; FTC and LMV; ADV and LMV and TFV; or ADV and FTC and TFV; TFV and FTC and LMV; ADV and LMV and FTC; and/or ADV and FTC and LMV and TFV and other nucleoside or nucleotide analogs and/or anti-HBV agents wherein the variant comprises a mutation in the surface protein selected from the list of sQ30K, sE44G, sA47T, sI126T, sA159V, sL173F, sF55S, sC/Stop69C, sC/Y76Y, sI/V110I, sN/T131N, sN134Y, sStop/W172W, sStop/W196W, sS/R207R, sV14A, sL95W, sV96G, sI208T/I, sL95W, sL196W, sT47A, sW172Stop, PreS2 T6S, sT47A, sP62L, sL/F192F, sI195M, sS53L, sL42R, SQ102Q/R, sT115T/S, sS207S/R, sL215R and sL216 stop.

19. An isolated HBV variant of Claim 18 wherein the variant comprises a mutation in the HBV DNA polymerase selected from the list consisting of rtT38K, rtA181V, rtR55H, rtY245H, rtS/T78S, rtV80L, rtN/S118N, rtN/K139K, rtE142V, rtA/T181A, rtI204M, rtQ/P/S/Stop215S, rtE/K21E, rtN/H238H, rtT128N, rtN236T, rtL180M, rtM204V, rtQ215S, rtT128S, rtN238T, rt180L, rtI204M, rtN238T, rtI187V, rtN248Q, rtS256G, rtI122V, rtA181T, rtL180M, rtA/V200V, rtM204V, rtV214A, rtH237H/P, rtV253G, rtN238T/A, rtN238T, rtN123N/I, rtS135Y, rtV214A/V and rtQ215Q/P/Stop/S.

20. The isolated HBV variant of Claim 18 or 19 wherein the decreased sensitivity is in respect of ADV.

21. The isolated HBV variant of Claim 18 or 19 wherein the decreased sensitivity is in respect of LMV.

22. The isolated HBV variant of Claim 18 or 19 wherein the decreased sensitivity is in respect of TFV.

23. The isolated HBV variant of Claim 18 or 19 wherein the decreased sensitivity is in respect of FTC.

24. The isolated HBV variant of Claim 18 or 19 wherein the decreased sensitivity is in respect of ADV and LMV.

25. The isolated HBV variant of Claim 18 or 19 wherein the decreased sensitivity is in respect of ADV and TFV.

26. The isolated HBV variant of Claim 18 or 19 wherein the decreased sensitivity is in respect of LMV and TFV.

27. The isolated HBV variant of Claim 18 or 19 wherein the decreased sensitivity is in respect of ADV and FTC.

28. The isolated HBV variant of Claim 18 or 19 wherein the decreased sensitivity is in respect of FTC and TFV.

29. The isolated HBV variant of Claim 18 or 19 wherein the decreased sensitivity is in respect of FTC and LMV.

30. The isolated HBV variant of Claim 18 or 19 wherein the decreased sensitivity is in respect of ADV and LMV and TFC.

31. The isolated HBV variant of Claim 18 or 19 wherein the decreased sensitivity is in respect of ADV and TFV and FTC.

32. The isolated HBV variant of Claim 18 or 19 wherein the decreased sensitivity is in respect of LMV and TFV and FTC.

33. The isolated HBV variant of Claim 18 or 19 wherein the decreased sensitivity is in respect of ADV and LMV and FTC.

34. The isolated HBV variant of Claim 18 or 19 wherein the decreased sensitivity is in respect of ADV and FTC and TFV and LMV.

35. A method for determining the potential for an HBV to exhibit reduced sensitivity to a nucleoside or nucleotide analog selected from ADV, LMV, TFV and FTC or optionally other nucleoside or nucleotide analogs, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV DNA polymerase resulting in at least one amino acid substitution, deletion and/or addition in any one or more of domains F and A through E or a region proximal thereto of said DNA polymerase and associated with resistance or decreases sensitivity to one or more of ADV, LMV, TFV and/or FTC wherein the presence of such a mutation is an indication of the likelihood of resistance to said one or more of ADV, LMV, TFV and/or FTC wherein the mutation screened for in the DNA polymerase is selected from the listing consisting of rtT38K, rtA181V, rtR55H, rtY245H, rtS/T78S, rtV80L, rtN/S118N, rtN/K139K, rtE142V, rtA/T181A, rtI204M, rtQ/P/S/Stop215S, rtE/K21E, rtN/H238H, rtT128N, rtN236T, rtL180M, rtM204V, rtQ215S, rtT128S, rtN238T, rt180L, rtI204M, rtN238T, rtI187V, rtN248Q, rtS256G, rtI122V, rtA181T, rtL180M, rtA/V200V, rtM204V, rtV214A, rtH237H/P, rtV253G, rtN238T/A, rtN238T, rtN123N/I, rtS135Y,

36. The method of an HBV of Claim 35 wherein the mutation screened for is in the surface protein selected from the list consisting of sQ30K, sE44G, sA47T, sI126T, sA159V, sL173F, sF55S, sC/Stop69C, sC/Y76Y, sI/V110I, sN/T131N, sN134Y, sStop/W172W, sStop/W196W, sS/R207R, sV14A, sL95W, sV96G, sI208T/I, sL95W, sL196W, sT47A, sW172Stop, PreS2 T6S, sT47A, sP62L, sL/F192F, sI195M, sS53L, sL42R, SQ102Q/R, sT115T/S, sS207S/R, sL215R and sL216 stop.

37. A method for determining whether an HBV strain exhibits reduced sensitivity to a nucleoside or nucleotide analog, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding the DNA polymerase wherein the presence of a mutation in a region selected from the F to G domain, between F and A domains, the A domain, between the A and B domains, the B domain, between the B and C domains, to C domain, between the C and D domains, the D domain, between the D and E domain and the E domain or combinations thereof or an equivalent one or more other mutation is indicative of a variant wherein said variant exhibits a decreased sensitivity to one or more of ADV, LMV, TFV and/or FTC optionally other nucleoside or nucleotide analogs wherein said variant comprises a mutation in the DNA polymerase selected from the list consisting of rtT38K, rtA181V, rtR55H, rtY245H, rtS/T78S, rtV80L, rtN/S118N, rtN/K139K, rtE142V, rtA/T181A, rtI204M, rtQ/P/S/Stop215S, rtE/K21E, rtN/H238H, rtT128N, rtN236T, rtL180M, rtM204V, rtQ215S, rtT128S, rtN238T, rt180L, rtI204M, rtN238T, rtI187V, rtN248Q, rtS256G, rtI122V, rtA181T, rtL180M, rtA/V200V, rtM204V, rtV214A, rtH237H/P, rtV253G, rtN238T/A, rtN238T, rtN123N/I, rtS135Y, rtV214A/V and rtQ215Q/P/Stop/S.

38. The method of Claim 37 wherein the variant comprises a mutation in the surface protein selected from the listing consisting of sQ30K, sE44G, sA47T, sI126T, sA159V, sL173F, sF55S, sC/Stop69C, sC/Y76Y, sI/V110I, sN/T131N, sN134Y, sStop/W172W, sStop/W196W, sS/R207R, sV14A, sL95W, sV96G, sI208T/I, sL95W, sL196W, sT47A, sW172Stop, PreS2 T6S, sT47A, sP62L, sL/F192F, sI195M, sS53L, sL42R, SQ102Q/R,

39. A method for detecting an agent which exhibits inhibitory activity to an HBV which exhibits resistance or decreased sensitivity to one or more of ADV, LMV, TFV and/or FTC said method comprising:

generating a genetic construct comprising a replication competent-effective amount of the genome from said HBV contained in a plasmid vector and then transfecting said cells with said construct;

contacting said cells, before, during and/or after transfection, with the agent to be tested;

culturing said cells for a time and under conditions sufficient for the HBV to replicate, express genetic sequences and/or assemble and/or release virus or virus-like particles if resistant to said agent; and

subjecting the cells, cell lysates or culture supernatant fluid to viral- or viral-component-detection means to determine whether or not the virus has replicated, expressed genetic material and/or assembled and/or been released in the presence of said agent,

wherein the HBV variant comprises a mutation in the DNA polymerase selected from the listing consisting of rtT38K, rtA181V, rtR55H, rtY245H, rtS/T78S, rtV80L, rtN/S118N, rtN/K139K, rtE142V, rtA/T181A, rtI204M, rtQ/P/S/Stop215S, rtE/K21E, rtN/H238H, rtT128N, rtN236T, rtL180M, rtM204V, rtQ215S, rtT128S, rtN238T, rt180L, rtI204M, rtN238T, rtI187V, rtN248Q, rtS256G, rtI122V, rtA181T, rtL180M, rtA/V200V, rtM204V, rtV214A, rtH237H/P, rtV253G, rtN238T/A, rtN238T, rtN123N/I, rtS135Y, rtV214A/V and rtQ215Q/P/Stop/S.

40. The method of Claim 39 wherein the HBV variant comprises a mutation in the surface protein selected from the list consisting of sQ30K, sE44G, sA47T, sI126T, sA159V, sL173F, sF55S, sC/Stop69C, sC/Y76Y, sI/V110I, sN/T131N, sN134Y, sStop/W172W, sStop/W196W, sS/R207R, sV14A, sL95W, sV96G, sI208T/I, sL95W, sL196W, sT47A, sW172Stop, PreS2 T6S, sT47A, sP62L, sL/F192F, sI195M, sS53L, sL42R, SQ102Q/R, sT115T/S, sS207S/R, sL215R and sL216 stop.

41. A computer product for assessing the likely usefulness of a viral variant or biological sample comprising same for determining an appropriate therapeutic protocol in a subject, said product comprising:

(1) code that receives as input code for at least two features associated with said viral agents or biological sample comprising same, wherein said features are selected from:

(a) the ability to exhibit resistance for reduced sensitivity to a particular compound or immunological agent;

(b) an altered DNA polymerase from wild-type HBV;

(c) an altered surface protein from wild-type HBV; or

(d) morbidity or recovery potential of a patient;

(2) code that adds said input code to provide a sum corresponding to a value for said viral variants or biological samples; and

(3) a computer readable medium that stores the codes;

wherein the altered DNA polymerase is selected from the list consisting of rtT38K, rtA181V, rtR55H, rtY245H, rtS/T78S, rtV80L, rtN/S118N, rtN/K139K, rtE142V, rtA/T181A, rtI204M, rtQ/P/S/Stop215S, rtE/K21E, rtN/H238H, rtT128N, rtN236T, rtL180M, rtM204V, rtQ215S, rtT128S, rtN238T, rt180L, rtI204M, rtN238T, rtI187V, rtN248Q, rtS256G, rtI122V, rtA181T, rtL180M, rtA/V200V, rtM204V, rtV214A, rtH237H/P, rtV253G, rtN238T/A, rtN238T, rtN123N/I, rtS135Y, rtV214A/V and rtQ215Q/P/Stop/S;

wherein the altered surface antigen is selected from the list consisting of sQ30K, sE44G, sA47T, sI126T, sA159V, sL173F, sF55S, sC/Stop69C, sC/Y76Y, sI/V110I, sN/T131N, sN134Y, sStop/W172W, sStop/W196W, sS/R207R, sV14A, sL95W, sV96G, sI208T/I, sL95W, sL196W, sT47A, sW172Stop, PreS2 T6S, sT47A, sP62L, sL/F192F, sI195M, sS53L, sL42R, SQ102Q/R, sT115T/S, sS207S/R, sL215R and sL216 stop.

42. A computer for assessing the likely usefulness of a variant or biological sample comprising same in a subject, wherein said computer comprises:

(1) a machine-readable data storage medium comprising a data storage material

codes for at least two features associated with said viral variant or biological sample; wherein said features are selected from:-

(a) the ability to exhibit resistance for reduced sensitivity to a particular compound or immunological agent;

(b) an altered DNA polymerase from wild-type HBV;

(c) an altered surface protein from wild-type HBV; or

(d) morbidity or recovery potential of a patient;

(2) a working memory for storing instructions for processing said machine-readable data;

(3) a central-processing unit coupled to said working memory and to said machine-readable data storage medium, for processing said machine readable data to provide a sum of said input code corresponding to a value for said compound(s); and

(4) an output hardware coupled to said central processing unit, for receiving said value;

wherein the altered DNA polymerase is selected from the list consisting of rtT38K, rtA181V, rtR55H, rtY245H, rtS/T78S, rtV80L, rtN/S118N, rtN/K139K, rtE142V, rtA/T181A, rtI204M, rtQ/P/S/Stop215S, rtE/K21E, rtN/H238H, rtT128N, rtN236T, rtL180M, rtM204V, rtQ215S, rtT128S, rtN238T, rtI80L, rtI204M, rtN238T, rtI187V, rtN248Q, rtS256G, rtI122V, rtA181T, rtL180M, rtA/V200V, rtM204V, rtV214A, rtH237H/P, rtV253G, rtN238T/A, rtN238T, rtN123N/I, rtS135Y, rtV214A/V and rtQ215Q/P/Stop/S;

wherein the altered surface antigen is selected from the list consisting of sQ30K, sE44G, sA47T, sI126T, sA159V, sL173F, sF55S, sC/Stop69C, sC/Y76Y, sI/V110I, sN/T131N, sN134Y, sStop/W172W, sStop/W196W, sS/R207R, sV14A, sL95W, sV96G, sI208T/I, sL95W, sL196W, sT47A, sW172Stop, PreS2 T6S, sT47A, sP62L, sL/F192F, sI195M, sS53L, sL42R, SQ102Q/R, sT115T/S, sS207S/R, sL215R and sL216 stop.

43. The computer product or composition of Claim 41 or 42 wherein the input code is resistant to one or more of ADV, LMV, TFV and/or FTC.

44. Use of an HBV variant in the manufacture of a medicament for the treatment or prophylaxis of HBV infection said HBV variant comprising a mutation in the DNA polymerase selected from the list consisting of rtT38K, rtA181V, rtR55H, rtY245H, rtS/T78S, rtV80L, rtN/S118N, rtN/K139K, rtE142V, rtA/T181A, rtI204M, rtQ/P/S/Stop215S, rtE/K21E, rtN/H238H, rtT128N, rtN236T, rtL180M, rtM204V, rtQ215S, rtT128S, rtN238T, rt180L, rtI204M, rtN238T, rtI187V, rtN248Q, rtS256G, rtI122V, rtA181T, rtL180M, rtA/V200V, rtM204V, rtV214A, rtH237H/P, rtV253G, rtN238T/A, rtN238T, rtN123N/I, rtS135Y, rtV214A/V and rtQ215Q/P/Stop/S and/or a mutation in the surface protein selected from the list consisting of sQ30K, sE44G, sA47T, sI126T, sA159V, sL173F, sF55S, sC/Stop69C, sC/Y76Y, sI/V110I, sN/T131N, sN134Y, sStop/W172W, sStop/W196W, sS/R207R, sV14A, sL95W, sV96G, sI208T/I, sL95W, sL196W, sT47A, sW172Stop, PreS2 T6S, sT47A, sP62L, sL/F192F, sI195M, sS53L, sL42R, SQ102Q/R, sT115T/S, sS207S/R, sL215R and sL216 stop.

45. Use of Claim 44 wherein the HBV variant is resistant to one or more of ADV, LMV, TFV and/or FTC.

46. A method for detecting a variant HBV exhibiting an altered immunological profile said method comprising isolating an HBV from a subject exposed to a nucleoside or nucleotide analog selected from the listed consisting of ADV, LMV, TFV or FTC; ADV and LMV; ADV and TFV; LMV and TFV; FTC and ADV; FTC and TFV; FTC and LMV; ADV and LMV and TFV; ADV and FTC and TFV; TFV and FTC and LMV; ADV and LMV and FTC; ADV and FTC and LMV and TFV, and then contacting said HBV with a panel of one or more antibodies to a surface antigen and screening for any change in binding affinity or binding spectrum said variant HBV comprising a mutation in the surface protein selected from the listing consisting of sQ30K, sE44G, sA47T, sI126T, sA159V, sL173F, sF55S, sC/Stop69C, sC/Y76Y, sI/V110I, sN/T131N, sN134Y, sStop/W172W, sStop/W196W, sS/R207R, sV14A, sL95W, sV96G, sI208T/I, sL95W, sL196W, sT47A, sW172Stop, PreS2 T6S, sT47A, sP62L, sL/F192F, sI195M, sS53L, sL42R, SQ102Q/R, sT115T/S, sS207S/R, sL215R and sL216 stop.

47. The method of Claim 46 wherein the variant HBV comprises a mutation in the DNA polymerase selected from the listing consisting of rtT38K, rtA181V, rtR55H, rtY245H, rtS/T78S, rtV80L, rtN/S118N, rtN/K139K, rtE142V, rtA/T181A, rtI204M, rtQ/P/S/Stop215S, rtE/K21E, rtN/H238H, rtT128N, rtN236T, rtL180M, rtM204V, rtQ215S, rtT128S, rtN238T, rt180L, rtI204M, rtN238T, rtI187V, rtN248Q, rtS256G, rtI122V, rtA181T, rtL180M, rtA/V200V, rtM204V, rtV214A, rtH237H/P, rtV253G, rtN238T/A, rtN238T, rtN123N/I, rtS135Y, rtV214A/V and rtQ215Q/P/Stop/S.

48. A kit for an assay for variant HBV resistant to ADV, LMV, TFV, or FTC; or ADV and LMV; ADV and TFV; LMV and TFV; FTC and ADV; FTC and TFV; FTC and LMV; or ADV and LMV and TFV; or ADV and FTC and TFV; TFV and FTC and LMV; ADV and LMV and FTC; or ADV and FTC and LMV and TFV, said kit comprising genetic agents capable of detecting an altered DNA polymerase gene and/or a altered surface antigen gene on the HBV variant wherein the altered DNA polymerase is selected from the list consisting of rtT38K, rtA181V, rtR55H, rtY245H, rtS/T78S, rtV80L, rtN/S118N, rtN/K139K, rtE142V, rtA/T181A, rtI204M, rtQ/P/S/Stop215S, rtE/K21E, rtN/H238H, rtT128N, rtN236T, rtL180M, rtM204V, rtQ215S, rtT128S, rtN238T, rt180L, rtI204M, rtN238T, rtI187V, rtN248Q, rtS256G, rtI122V, rtA181T, rtL180M, rtA/V200V, rtM204V, rtV214A, rtH237H/P, rtV253G, rtN238T/A, rtN238T, rtN123N/I, rtS135Y, rtV214A/V and rtQ215Q/P/Stop/S wherein the altered surface antigen is selected from the list consisting of sQ30K, sE44G, sA47T, sI126T, sA159V, sL173F, sF55S, sC/Stop69C, sC/Y76Y, sI/V110I, sN/T131N, sN134Y, sStop/W172W, sStop/W196W, sS/R207R, sV14A, sL95W, sV96G, sI208T/I, sL95W, sL196W, sT47A, sW172Stop, PreS2 T6S, sT47A, sP62L, sL/F192F, sI195M, sS53L, sL42R, SQ102Q/R, sT115T/S, sS207S/R, sL215R and sL216 stop.

49. A kit for an assay for variant HBV resistant to ADV, LMV, TFV, or FTC; or ADV and LMV; ADV and TFV; LMV and TFV; FTC and ADV; FTC and TFV; FTC and LMV; or ADV and LMV and TFV; or ADV and FTC and TFV; TFV and FTC and LMV; ADV and LMV and FTC; or ADV and FTC and LMV and TFV, said kit comprising peptide or

surface antigen comprising a mutation selected from the list consisting of sQ30K, sE44G, sA47T, sI126T, sA159V, sL173F, sF55S, sC/Stop69C, sC/Y76Y, sI/V110I, sN/T131N, sN134Y, sStop/W172W, sStop/W196W, sS/R207R, sV14A, sL95W, sV96G, sI208T/I, sL95W, sL196W, sT47A, sW172Stop, PreS2 T6S, sT47A, sP62L, sL/F192F, sI195M, sS53L, sL42R, SQ102Q/R, sT115T/S, sS207S/R, sL215R and sL216 stop.

50. A method for determining the potential for an HBV to exhibit reduced sensitivity to ADV, LMV, TFV, or FTC; or ADV and LMV; ADV and TFV; LMV and TFV; FTC and ADV; FTC and TFV; FTC and LMV; or ADV and LMV and TFV; or ADV and FTC and TFV; TFV and FTC and LMV; ADV and LMV and FTC; or ADV and FTC and LMV and TFV and/or optionally other nucleoside or nucleotide analogs or other anti-HBV agents or combination thereof, said method comprising isolating DNA or corresponding mRNA from said HBV and screening for a mutation in the nucleotide sequence encoding HBV DNA polymerase resulting in at least one amino acid substitution, deletion and/or addition in any one or more of domains F and G, and domains A through to E or a region proximal thereto of said DNA polymerase and associated with resistance or decreased sensitivity to ADV, LMV, TFV, or FTC; or ADV and LMV; ADV and TFV; LMV and TFV; FTC and ADV; FTC and TFV; FTC and LMV; or ADV and LMV and TFV; or ADV and FTC and TFV; TFV and FTC and LMV; ADV and LMV and FTC; or ADV and FTC and LMV and TFV, wherein the presence of such a mutation is an indication of the likelihood of resistance to said ADV, LMV, TFV, or FTC; or ADV and LMV; ADV and TFV; LMV and TFV; FTC and ADV; FTC and TFV; FTC and LMV; or ADV and LMV and TFV; or ADV and FTC and TFV; TFV and FTC and LMV; ADV and LMV and FTC; or ADV and FTC and LMV and TFV wherein the HBV comprises a DNA polymerase having a mutation selected from the list consisting of rtT38K, rtA181V, rtR55H, rtY245H, rtS/T78S, rtV80L, rtN/S118N, rtN/K139K, rtE142V, rtA/T181A, rtI204M, rtQ/P/S/Stop215S, rtE/K21E, rtN/H238H, rtT128N, rtN236T, rtL180M, rtM204V, rtQ215S, rtT128S, rtN238T, rtI80L, rtI204M, rtN238T, rtI187V, rtN248Q, rtS256G, rtI122V, rtA181T, rtL180M, rtA/V200V, rtM204V, rtV214A, rtH237H/P, rtV253G, rtN238T/A, rtN238T, rtN123N/I, rtS135Y, rtV214A/V and rtQ215Q/P/Stop/S.

51. The method of Claim 50 wherein the HBV comprises a surface antigen having a mutation selected from the list consisting of sQ30K, sE44G, sA47T, sI126T, sA159V, sL173F, sF55S, sC/Stop69C, sC/Y76Y, sI/V110I, sN/T131N, sN134Y, sStop/W172W, sStop/W196W, sS/R207R, sV14A, sL95W, sV96G, sI208T/I, sL95W, sL196W, sT47A, sW172Stop, PreS2 T6S, sT47A, sP62L, sL/F192F, sI195M, sS53L, sL42R, SQ102Q/R, sT115T/S, sS207S/R, sL215R and sL216 stop.

52. A vaccine comprising an agent selected from a surface component of a variant HBV as defined in any one of Claims 1 to 34; a combination of a variant HBV as defined in any one of Claims 1 to 34 and another anti-HBV agent; and an agent inhibitory to a variant HBV as defined in any one of Claims 1 to 34.